REMARKS/ARGUMENTS

I. Status of the Claims

Claims 69 and 70 are pending in the present application. Claims 62 and 68 have been canceled without prejudice or disclaimer. Applicants reserve the right to file one or more applications directed to this canceled subject matter.

II. Telephonic Interview

Applicants thank Examiner Shukla for the telephonic interview held with Applicants' attorney, Anne Brown, Youssef Bennani, Ph.D., Senior Director of Medicinal Chemistry at Athersys, Inc., Biotechnology Specialist Brian Stanton, and Supervisory Examiner Deborah Reynolds on May 12, 2004. In that interview, Applicants explained that a Declaration addressing the points in the written description rejection was submitted previously with Applicants' Response dated July 10, 2003. Mr. Stanton suggested that Applicants refer to that Declaration in the present Response. Accordingly, Applicants do so below.

In the interview the enablement rejection was also discussed. Applicants presented a schematic showing why, for compound testing, it is not necessary to know what gene (or genes) is responsible for an activated phenotype. Applicants also presented a schematic showing why no undue experimentation is required to activate a desired gene and test a compound for interaction with that gene. Applicants were advised to present those arguments in their Response. Accordingly, Applicants do so below.

Finally, Dr. Bennani discussed the fact that drug discovery is commonly done without knowing specific structure-function relationships for compounds and gene products. He indicated that it is common in the industry to take an "off the shelf" approach by randomly selecting compounds for testing. This is also addressed below.

III. The Rejections

A. Rejection of claims 62 and 68-70 under 35 U.S.C. §112, first paragraph, written description.

On page 2 of the Office Action claims 62 and 68-70 are rejected on the grounds that they contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors were in possession of the claimed invention. Applicants respectfully traverse the rejection.

Citations In Text

On page 3 of the Office Action the Examiner states that the only references to the term "drug discovery" are found on page 7, lines 28-30 and page 11, lines 27-29 continued through page 12, lines 1 and 2. Applicants point out that the specification refers to drug discovery in more areas. In addition to the text cited by the Examiner, reference to use of the invention for drug discovery is also found on page 32, lines 1-6, page 35, lines 26-30 and page 69, lines 14-18. Applicants have also referenced the disclosure in Applicants' earliest priority application 09/941,223 in page 5, last paragraph, page 9, fourth paragraph, page 12, last paragraph, page 16, second paragraph and page 45, third paragraph.

There Is Adequate Written Description For The Claim As A Whole

On page 3 of the Office Action the Examiner sets forth the rationale for the rejection. He states that the specification does not provide written support steps (a)–(e). Applicants respectfully disagree for the reasons that follow.

In the interview, Examiner Shukla and Supervisory Examiner Reynolds took the position that the specification does not describe the claim as a whole, i.e., the combination of steps (a)-(c) with steps (d)-(e). The Examiners took the position that ANY disclosure of using the RAGE technology for compound testing would, at best, be limited to testing a compound against a purified protein, not a cell.

Applicants have previously addressed this position with a qualified Declaration from a third party with expertise in the field of drug discovery. Applicants' Response dated July 10, 2003. The party had reviewed the specification and commented on whether the specification would have reasonably conveyed to the person of ordinary skill in the art that Applicants had possession of an invention in which cells expressing activated genes were screened against a test compound (i.e., combine steps (a)-(c) with steps (d)-(e)).

Third Party Expert Declaration

The Examiner is, therefore, directed to the Declaration of Dale Dhanoa, Ph.D., Senior Vice President Research and Discovery, Predix Pharmaceuticals. In the Declaration, Dr. Dhanoa

commented on what he thought was described in Applicants' application with respect to drug discovery in the context of the disclosed activation technology. Dr. Dhanoa stated that the drug discovery process would involve, at a minimum, screening a test compound for its effect. He indicated that typically two approaches were commonly used to assess the end point. These included protein-based screening and cell-based screening. He stated that although *in vitro* screening of a test compound against a protein outside of the cell was used, a whole cell assay was actually a better measure of the performance of test compounds when one tested for the effect of the compound on a cellular process. He stated that, in fact, screening compounds in cell-based assays was a more efficient process.

He stated that what the specification described was that cells can be cultured in vitro and cells that express an activated gene can be used in the drug discovery process. This means that the whole cell would be exposed to a test compound and the effect of the compound would be assessed. Dr. Dhanoa also stated that he believes, as an expert, he is qualified to speak to what the person of ordinary skill in the field would have realized to be described in the application, namely to expose a test compound to a gene product, both *in vitro* and in a whole cell assay. Accordingly, he concluded that a person of ordinary skill in the field of drug discovery, reading the application, would have realized that the Applicants, by disclosing the drug discovery process, were, in fact, describing the claimed method.

Dr. Dhanoa referred to disclosure in 08/941,223. This is the earliest priority application. For the Examiner's convenience, Applicants point out the same disclosure in the present application, 09/484,331: 7:25-30; 11:27-30; 12:1-2; 32:3-6; 35:26-30; 69:14-18.

Based on the Declaration discussed above, Applicants believe that the grounds for rejection have been addressed and the rejection on these grounds overcome. Reconsideration and withdrawal of the rejection of the claims as lacking adequate written description is, therefore, respectfully requested.

B. Rejection of Claims 62 and 68-70 under 35 U.S.C. §112 first paragraph, enablement.

On page 3 of the Office Action claims 62 and 68-70 have been rejected under 35 U.S.C. §112, first paragraph, on the grounds that the claimed subject matter is not enabled. Applicants respectfully traverse the rejection.

Specifically, on page 2 of the Office Action, the Examiner states that these claims are not enabled "because step (e) lacks enablement". Step (e), however, is not the only issue. Step (a) is at issue.

Step (a)

On page 5 of the Office Action, the Examiner states that step (a) encompasses activation by homologous recombination. This objection, however, would apply only to claim 62. Claim 69 is directed to non-targeted activation. Claim 62 has been canceled. Therefore, the rejection on this ground is moot.

Step (e); "Desired Gene"

On page 5 of the Office Action the Examiner indicates that it would have been routine to practice steps (b)–(d) of the claimed method, but asserts that it would not have been routine to practice step (e). The Examiner indicates that an artisan "would need to know the structure of the compound, structure of the gene product and requirements for the interaction of the compound to interact with a gene product".

On page 6 the Examiner summarizes the rationale as follows "in the absence of any teaching in the specification, an artisan of skill would not have been able to determine whether the product of the activated gene interacts with a test compound when the activated gene is *random, unknown and uncharacterized*". Italics added. Applicants disagree because the claim does not recite that interaction would be with an unknown and/or uncharacterized gene. Interaction is claimed only for a "desired" gene, a gene chosen in advance of testing.

This rationale for non-enablement was previously set forth in the Office Action dated April 28, 2000. See pages 4-7. The rejection was withdrawn when Applicants amended the claim to refer to "desired" gene at the suggestion of Mr. Priebe.

"Desired gene" means that a gene of interest is chosen in advance of testing and cells are screened for that gene. Therefore one would use the available assays specific for that gene. For example, if the desired gene is GMCSF, an assay is applied for GMCSF. If the desired gene is insulin, an assay is applied for insulin.

The Applicants provide Exhibit A showing the case in which a desired gene (GMCSF) is activated. A. A vector is integrated into cells and in one of those cells the vector integrates around the GMCSF gene. B. The cells are screened for a cell expressing GMCSF. C. A cell expressing GMCSF is selected. D. The cell is exposed to a test compound and an assay is applied based on GMCSF to ascertain whether the compound interacts with GMCSF.

The Examiner further states (Office Action, page 6) "the specification does not teach as to how an artisan would have determined that a compound, in step (e), interacted with the gene product of the desired gene, not with the product of any other gene". Applicants point out that the claimed assay is inherently limited to interaction of the compound *with the desired product.* Thus, if the compound interacted with a non-desired product, the claim would not apply.

The Examiner may be concerned that even if a "desired" gene is expressed, expression could be a secondary effect and not the direct effect of vector insertion. First, Applicants point out that even if indirect activation were to occur, the claim literally covers this embodiment. Second, even if the claim were to be construed as limited to direct activation by vector insertion, direct activation events would be expected to occur, and *do* occur, based on data in the application.

The application shows the production of chimeric RNAs. See page 135 of Applicants' specification. This shows direct vector activation of desired genes (in this case, transmembrane proteins). Therefore, it is reasonably predictable that a desired gene will be directly activated by vector insertion. In fact, in further application of the claimed technology, Applicants have found

that in 8-9 out of 10 randomly selected genes, direct activation takes place. Also, Applicants have created over 20 cell lines expressing desired genes and have verified in every case that genes were directly activated by vector insertion (i.e., produced hybrid mRNA containing vector and endogenous gene sequences). This shows direct activation of desired genes by the vector promoter.

Step (e); Desired Phenotype

Alternatively, instead of detecting a specific desired gene, step (e) is also directed to cells that are screened for the activation of a specific desired phenotype. On page 6 the Examiner states that "even when a cell in which a desired gene is activated, there is no way of knowing if the desired phenotype observed in a selected cell is due to the activated expression of only the desired gene or due to an activation of multiple genes". Applicants point out that the gene or genes causing the phenotype, directly or indirectly, are irrelevant. To practice the claimed compound testing the artisan need not know what genes are involved. The claim is simply directed to testing a compound for its effect on the phenotype. Thus, in this case, the phenotype could be caused by a characterized gene, an uncharacterized gene, one or more genes, directly or indirectly.

If for example, one was interested in activating the phenotype of drug resistance, one introduces vectors into cells and then screens for drug resistance in the progeny cell. Having created a cell that was drug resistant, *without reference to any gene causing the phenotype*, one could expose that cell to a compound and ascertain whether it increased or diminished drug resistance (i.e., the activated phenotype).

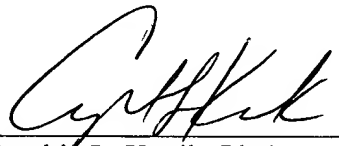
Applicants have provided Exhibit B showing the process of activating a desired phenotype and exposing a cell with the activated phenotype to a test compound. A. Vectors are integrated into cells and in one case a drug resistant cell is produced. B. The cells are then screened for a cell having that phenotype. C. The cell having the phenotype is selected. D. The cell with the phenotype is exposed to a test compound and the effect of that compound on the phenotype is then assessed. It can be seen that the gene or genes causing the phenotype need not be known. All that is required is a cell having a non-parental phenotype which is useful when the phenotype arises directly or indirectly from vector insertion.

Knowledge of Structure-Function Relationship

With respect to a requirement for compounds with specific chemical structures, in the interview Dr. Bennani pointed out that drug discovery is routinely done using random compound libraries, irrespective of the structure of those compounds. This is a technique common in the drug discovery industry. Basically, compounds are randomly selected off the shelf and exposed to cells to assess the compound's effect on gene products or phenotypes. Applicants have also addressed this requirement in a previous Declaration by Dr. Bennani. The Examiner is, therefore, referred to that Declaration submitted with the Office Action dated April 25, 2002.

Accordingly, Applicants believe that they have addressed each of the grounds of the rejection and the rejection has been overcome. Reconsideration and withdrawal of the rejection is, therefore, respectfully requested.

Respectfully submitted,



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